REMARKS/ARGUMENTS

After the above amendments, Claims 1-26, 28-31 and 375-381 are pending. Support for the amendments to Claim 1 may be found at, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application.

A. Objections to the Specification

On page 6, line 7, of the specification, the Examiner has asked that the web address be deleted because such addresses are transient. Applicants do not believe it is necessary to do so since an alternate citation is provided (the abstracts of the Speciation 98 meeting). However, in the interests of advancing prosecution, Applicants have amended page 6 as indicated above to delete the reference to the web address.

The Examiner has also pointed out an error in Figures 1A-1D. Applicants are submitting herewith an amended drawing of Figures 1A-1D to correct this obvious error. Applicants apologize that a corrected drawing was not submitted with Applicants' previous response. However, contrary to the Examiner's contention, Applicants did acknowledge this issue in their previous response.

B. Double Patenting Rejection

The Examiner has rejected Claim 1 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of co-pending application Serial No. 10/186,168. This rejection is respectfully traversed, since Claim 1 of application Serial No. 10/186,168 has been canceled. Accordingly, the Examiner is asked to withdraw this rejection.

C. Section 112 Rejection

The Examiner has rejected Claims 21-24, 28-30 and 375-381 on the basis that they are indefinite because they are dependent on non-elected claims. Applicants are not entirely clear

about the Examiner's reasons for this rejection, but believe that these claims are being rejected because they depend, in part, on currently withdrawn Claims 12-20. However, Claims 12-20 are withdrawn only because they are not drawn to elected species. Applicants expect that Claims 12-20 will ultimately be rejoined with the rest of the claims and examined, and so Applicants have kept the claims directed to non-elected species in the case and have amended along with the claims directed to the elected species. See MPEP § 809.02(c). Accordingly, it is submitted that this rejection is premature, and Applicants will not amend Claims 21-24, 28-30 and 375-381 at this time.

D. Section 103 Rejections

1. Rejection of Claims 1, 9-10, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 9-10, 21-24, 28-30 and 375-381 as being unpatentable over Deghenghi (U.S. Patent No. 5,932,548). It is the Examiner's position that:

> Deghenghi discloses (col 4, line 10) the following peptide:
> Tyr-Ala-His-D-Mrp-Ala-Trp-D-Phe-Lys-NH_2
> Also disclosed is that this is one of several peptides that is useful for treatment of myocardial ischemia. Accordingly, whatever damage is caused by ROS (or any other molecular entities) in the manifestations of ischemia will be mitigated.
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Deghenghi teaches the use of certain lysine-containing peptides, including the specific Tyr-Ala-His-D-Mrp-Ala-Trp-D-Phe-Lys-NH_2 peptide, for normalizing cardiac pressure for the treatment of heart disease (see column 1, lines 35-38). The term heart disease is used to refer to a variety of cardiac disorders, including myocardial ischemia, heart failure and related vascular dysfunction (see column 1, lines 8-10). Deghenghi teaches that the mechanism by which the peptides normalize cardiac pressure is unknown (see column 1, lines 44-48).

The Examiner contends that, since the Tyr-Ala-His-D-Mrp-Ala-Trp-D-Phe-Lys-NH_2 peptide can be used to treat myocardial ischemia, "whatever damage is caused by ROS (or any other molecular entities) in the manifestations of ischemia will be mitigated." However, there is no teaching or suggestion in Deghenghi that the Tyr-Ala-His-D-Mrp-Ala-Trp-D-Phe-Lys-NH_2 peptide, or any of the others taught by that patent, reduce ROS or the damage done by ROS, or that normalizing cardiac pressure would do so. Indeed, Deghenghi does not teach or suggest anything about ROS, and Deghenghi expressly teaches that the mechanism by which the peptide normalizes cardiac pressure is unknown.

Quite clearly, then, there is no basis in Deghenghi for the Examiner's contentions about ROS or the damage they do. It is submitted that the only possible source of such information is Applicants' disclosure, and that the Examiner is improperly reconstructing the claimed invention through hindsight using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner has not met in this case.

Most important, however, Deghenghi does not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by Deghenghi.

For all of the foregoing reasons, the teachings of Deghenghi would not have made the claimed invention obvious, and the Examiner is asked to withdraw this rejection.

2. Rejection of Claims 1, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 21-24, 28-30 and 375-381 as being unpatentable over Rosenzweig (PCT application WO 00/23469). It is the Examiner's position that:

> Rosenzweig discloses (page 26, line 21) a method of treating ischemic injury by administering any of several peptides. Among those are the peptides designated SEQ ID NO: 6, 15, 16, 29-34 and 37, all of which have a histidine at the requisite position. Thus, the artisan of ordinary skill would reason that if the peptides are effective to treat ischemic injury, then it will necessarily be true that the "damage" which gave rise to the ischemic injury is mitigated as well.
>
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Rosenzweig teaches certain peptides, including SEQ ID NOS: 6, 15, 16, 29-34 and 37, which are the isolated binding domains of insulin-like growth factor binding peptide (IGFBP) (see page 13, line 10 through page 18, line 21). These peptides are referred to as antagonists of insulin-like growth factor (IGF) because they bind to IGF, thereby reducing the amount of circulating IGF and the amount of binding of IGF to IGF receptors (see page 20, line 16 through page 22, line 16). Since they reduce the amount of circulating IGF and the amount of binding of IGF to IGF receptors, they are effective to treat diseases wherein a reduction in IGF and IGF binding to its receptors would be beneficial, such as cancer (see page 25, line 6 through page 26, line 20).

It is not these peptides, however, that are used to treat ischemic injury according to Rosenzweig. The peptides used to treat ischemic injury are fragments of IGF referred to as IFGBP antagonists because they bind to IGFBP, thereby increasing the amount of IGF (see page 23, line 13 through page 24, line 9, and page 26, line 22 through page 27, line 12). Thus, the peptides having SEQ ID NOS: 6, 15, 16, 29-34 and 37 are not taught by Rosenzweig for the treatment of ischemic injury, and the basis underlying the Examiner's rejection is factually incorrect. Accordingly, this rejection should be withdrawn

3. Rejection of Claims 1, 3, 9, 21-24 and 28-30

The Examiner has rejected Claims 1, 3, 9, 21-24 and 28-30 as being unpatentable over Liotta et al. (U.S. Patent No. 5,270,447) in view of Malins (*Proc. Nat'l Acad. Sci.*, **93**, 2557 (1996)) or Knight (*Ann. Clin. Lab. Sci.*, **25**, 111 (1995)). It is the Examiner's position that:

> Liotta et al. discloses (figure 6; col 5, line 3; table I, cols 5-6) the following peptide:
>
> AAHEEICTTNEGVM
>
> Also disclosed (e.g., col 15, line 56+) is that the peptide can be used to treat cancer. Liotta et al. does not disclose that tumor cell growth is caused by reactive oxygen species. Malins and Knight both disclose that tumor cell growth is caused at least in part by reactive oxygen species. Neither of Malins and Knight discloses a peptide falling within the scope of instant claim 1.
>
> One of ordinary skill in the art would expect that if cancer is caused by ROS, or if tumor cells give rise to ROS (or if both is true), then eliminating (at least in part) the tumor cells can only take place if the damage caused by the ROS has been mitigated. It may be the case that Liotta does not teach that the disclosed peptides act to directly reduce the formation of ROS. However, given that tumor cells increase the level of ROS, it follows therefrom that if the population of tumor cells is reduced, the amount of ROS produced by the tumor cells will be reduced as well. If the amount of ROS that is produced declines, then it stands to reason that the "damage" caused by those ROS's will also decline.
>
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Liotta et al. teaches certain peptides, including AAHEEICTTNEGVM, are inhibitors of metalloproteases (see column 4, line 57 through column 5, line 9). As a consequence of their ability to inhibit metalloproteases, it is suggested that AAHEEICTTNEGVM and the other peptides taught by Liotta et al., would be of use in the treatment of "tumor growth, invasion and metastasis" (see column 15, lines 56-60). There is no teaching or suggestion in Liotta et al. that AAHEEICTTNEGVM, or any of the other peptides taught by Liotta et al., reduce ROS or reduce the damage done by ROS. In fact, Liotta et al. does not teach or suggest anything about ROS.

Knight teaches that ROS may be able to induce neoplastic transformation of cells because of the changes and damage that they can cause in cellular DNA. Malins teaches that amount and

type of damage done to DNA by hydroxyl radicals have been statistically correlated to the possibility of metastasis of tumor cells and to the diversity of phenotypes of metastatic cells. Neither Knight nor Malins teaches or suggests anything about metalloprotease inhibitors.

As can be readily seen from the foregoing, the Examiner has provided no teaching, suggestion or motivation for combining the teachings of Liotta et al. with those of Malins and Knight. In particular, as noted above, Liotta et al. does not teach or suggest anything about ROS, and Knight or Malins do not teach or suggest anything about metalloprotease inhibitors. Presumably, the Examiner's rationale for choosing the cited references was that they all deal with the subject of cancer. However, why didn't the Examiner choose a reference discussing the role of oncogenes or some other factor in cancer instead of Knight and Malins which discuss the role of ROS in cancer?

It is submitted that the only basis for combining the teachings of Liotta et al. with those of Malins and Knight is improper hindsight reconstruction of the claimed invention by the Examiner using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner could not meet in this case.

Most important, however, the cited references, alone or in combination, do not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by Liotta et al. in combination with Knight or Malins.

For all of the foregoing reasons, the Examiner is asked to withdraw this rejection.

4. Rejection of Claims 1, 3, 9-10, 21-24 and 28-30

The Examiner has rejected Claims 1, 3, 9-10, 21-24 and 28-30 as being unpatentable over Blaschuk (U.S. Patent No. 6,610,821) in view of Malins (*Proc. Nat'l Acad. Sci.*, **93**, 2557 (1996)) or Knight (*Ann. Clin. Lab. Sci.*, **25**, 111 (1995)). It is the Examiner's position that:

> Blaschuk discloses various peptides falling within the scope of instant claim 1 including (col 4, line 11) SEQ ID NO: 36, which has the following sequence:
>
> Cys-Ser-**His**-Ala-Val-Cys
>
> It is also true that there is an acetyl group bonded to the N-terminus, and the two cysteine sulfhydryl groups are bonded together in [a] disulfide linkage. Blaschuk also discloses that the compounds are effective to reduce tumor cell angiogenesis and to reduce tumor cell volume.
>
> Blaschuk does not disclose that tumor cell growth is caused by reactive oxygen species. Malins and Knight both disclose that tumor cell growth is caused at least in part by reactive oxygen species. . . .
>
> The first issue concerns the structure of the peptide itself. . . . Claim 1 can be reasonably interpreted as encompassing any peptide as long as the "sequence" of that peptide falls within the scope of "P_1-P_2" (as these variables are defined). Claim 1 would therefor [sic] permit any substituent to be bonded to the *alpha*-amino group of Xaa_1, provided that the substituent is not itself an amino acid or peptide. If, for example an acetyl group were bonded to the *alpha*-amino group of Xaa_1, the "sequence" (*per se*) of the peptide "P_1-P_2" would not be affected one way or another. . . .
>
> The next issue concerns that of "damage" due to ROS, versus the teachings of the reference with regard to efficacy. The reference discloses that the peptides are effective to reduce tumor cell volumes by inhibiting angiogensis. However, the oncologist of ordinary skill would reason that tumor cells give rise to ROS, and so if fewer tumor cells are present, a smaller quantity of ROS will be produced. If a smaller quantity of ROS is produced, it stands to reason that the "damage" caused by those ROS's will also decline.
>
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Blaschuk teaches that certain cyclic peptides, including Ac-Cys Ser His Ala Val Cys, are modulators of cadherin-mediated endothelial cell adhesion (see column 3, line 5 through column 4, line 37). As a consequence of their ability to modulate cadherin-mediated endothelial cell adhesion, it is suggested that the cyclic peptides would be of use in the inhibition of angiogenesis

(Ac-Cys Ser His Ala Val Cys is not listed for this purpose) (see column 26, lines 24-67) and in the treatment of cancer (Ac-Cys Ser His Ala Val Cys is listed for this purpose) (see column 27, line 24 through column 28, line 15). There is no teaching or suggestion in Blaschuk that Ac-Cys Ser His Ala Val Cys, or any of the other cyclic peptides taught by Blaschuk, reduce ROS or reduce the damage done by ROS. In fact, Blaschuk does not teach or suggest anything about ROS.

Knight teaches that ROS may be able to induce neoplastic transformation of cells because of the changes and damage that they can cause in cellular DNA. Malins teaches that amount and type of damage done to DNA by hydroxyl radicals have been statistically correlated to the possibility of metastasis of tumor cells and to the diversity of phenotypes of metastatic cells. Neither Knight nor Malins teaches or suggests anything about cadherin-mediated endothelial cell adhesion modulators.

As can be readily seen from the foregoing, the Examiner has provided no teaching, suggestion or motivation for combining the teachings of Blaschuk with those of Malins and Knight. In particular, as noted above, Blaschuk does not teach or suggest anything about ROS, and Knight or Malins do not teach or suggest anything about cadherin-mediated endothelial cell adhesion modulators. Presumably, the Examiner's rationale for choosing the cited references was that they all deal with the subject of cancer. However, why didn't the Examiner choose a reference discussing the role of oncogenes or some other factor in cancer instead of Knight and Malins which discuss the role of ROS in cancer?

It is submitted that the only basis for combining the teachings of Blaschuk with those of Malins and Knight is improper hindsight reconstruction of the claimed invention by the Examiner using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner could not meet in this case.

Most important, however, the cited references, alone or in combination, do not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by Liotta et al. in combination with Knight or Malins.

Finally, it is the Examiner's position that: "Claim 1 would therefor [sic, therefore] permit any substituent to be bonded to the *alpha*-amino group of Xaa_1, provided the substituent is not itself an amino acid or peptide." This is not correct. Although Xaa_1 can be substituted (see, *e.g.*, page 17, lines 3-11, of the present application), the α-amino group of Xaa_1 cannot be substituted. If this group is substituted, as by an acetyl group, the ability of the peptide to effectively bind metal ions is lost, as is the ability of the peptide to reduce ROS and the damage done by ROS (see Example 10, especially Table 11, page 60, of the present application). Accordingly, Claim 1 has been amended to clarify that the α-amino group of Xaa_1 cannot be substituted.

For all of the foregoing reasons, the Examiner is asked to withdraw this rejection.

5. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over U.S. Patent No. 4,461,724 ("Konishi") in view of Ben-Hamida *(Inflammation Research: Official Journal of the European Histamine Research Society*, **47**(4):193-199 (1998)) or Danielsson *(Digestive Diseases and Sciences*, **43**(9 Suppl):167S-173S (1998)) or Iinuma *(Digestive Diseases and Sciences*, **43**(8):1657-1664 (1998)) or Manjari *(Prostaglandins, Leukotrienes and Essential Fatty Acids*, **59**(6):401-406 (1998)) or Norgaard *(Journal Of Infectious Diseases*, **174**(3):544-551 (1996)). It is the Examiner's position that:

> . . . Konishi discloses the use of peptides for treating ulcers. The peptides contain a histidine residue which is located 3 amino acids from the N-terminus, as required of the instant claims. Konishi does not disclose that the symptoms of ulcers are mediated by "ROS". Each of Ben-Hamida, Danielsson, Iinuma, Manjari and Norgaard disclose that ulcers are mediated by "ROS".
>
> As indicated, Konishi does not teach that the anti-ulcer effect derives directly from inhibiting the production of ROS. However, each of the secondary references discloses that the presence of *Helicobacter* gives rise (directly or indirectly) to production of ROS. Thus, perhaps the peptides of Konishi are acting by sequestering metal ions, leading to decrease ROS production. Or perhaps the peptides of Konishi inhibit one of the cellular processes of *Helicobacter*, leading to decreased proliferation of the bacteria which in turn leads to decreased production of ROS. Or perhaps the peptides act by inhibiting neutrophil oxidase. Or perhaps the peptides do not actually inhibit the production of ROS, but instead accelerate healing of the affected tissues. Regardless of which of these mechanisms may be acting, the result is that the "damage" caused by the ROS will be mitigated if the peptides are in fact effective to successfully treat patients afflicted with ulcers.
>
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Konishi does teach the use of certain peptides having a histidine as the third amino acid from the N-terminus for the treatment of ulcers. However, Konishi does not teach or suggest that these peptides reduce ROS or reduce the damage done by ROS. Indeed, Konishi does not teach or suggest anything about ROS.

The Examiner contends that each of Ben-Hamida, Danielsson, Iinuma, Manjari and Norgaard "disclose that ulcers are mediated by 'ROS'". The Examiner also contends that each of these references "discloses that the presence of *Helicobacter* gives rise (directly or indirectly) to production of ROS." Applicants disagree with the Examiner's contentions. The teachings of the references actually vary considerably, and some of them conflict with the Examiner's contentions. For instance, Norgaard teaches that the neutrophils of patients infected with *Helicobacter pylori* do <u>not</u> release ROS in response to stimulation by the infecting strain. Danielsson also teaches that only some strains of *H. pylori* have the ability to activate neutrophils to an oxidative burst (see Abstract). Danielsson does teach that these strains were more often

isolated from patients with peptic ulcer disease and active chronic gastritis (see Abstract), but reminds that the "pathogenesis of *Helicobacter pylori*-associated gastroduodenal disease is not yet well understood" (see first paragraph of text on page 167S). Ben-Hamida suggests that histamine, xanthine oxidase-induced oxygen free radicals and *H. pylori* may be associated with each other in chronic duodenal ulcers (see Abstract and final four paragraphs, columns 1-2, page 197). Manjari suggests that increased levels of ROS, antioxidants, nitric oxide and polyunsaturated fatty acids may play a role in duodenal ulcer (see abstract and third full paragraph of first column on page 405) and reports that the aetiology of peptic ulcer disease is multifactorial (see first full paragraph of text on page 401). Finally, Iinuma reports that the results described in that reference suggest that lipid peroxidation, mediated by ROS generated from xanthine oxidase and polymorphonuclear cells, plays an important role in the pathogenesis of duodenal ulcers induced by mepirizole in rats (see Abstract). It is submitted that, the teachings of these references, as a whole, teach that ulcers are mediated by many factors and, at best, suggest a possible role for ROS, among the other factors, in ulcers.

In any event, the teachings of the cited references, alone or in combination, would not have made the claimed method obvious. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS is not taught or suggested by Konishi in combination with one, or any combination, of Ben-Hamida, Iinuma, Manjari, Danielsson and/or Norgaard

Further, as can be readily seen from the foregoing, the Examiner has provided no teaching, suggestion or motivation for combining the teachings of Konishi with those of Ben-Hamida, Iinuma, Manjari, Danielsson and/or Norgaard. Presumably, the Examiner's rationale

for choosing the cited references was that they all deal with the subject of ulcers. However, why didn't the Examiner choose a reference discussing another aspect of ulcers, such as the role of acid in ulcers, instead of Ben-Hamida, Iinuma, Manjari, Danielsson and/or Norgaard which discuss the role of ROS in ulcers? It is submitted that the only basis for combining the teachings of Konishi with those of Ben-Hamida, Iinuma, Manjari, Danielsson and/or Norgaard is improper hindsight reconstruction of the claimed invention by the Examiner using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner could not meet in this case.

For all of the foregoing reasons, this rejection should be withdrawn.

6. Rejection of Claims 1, 4, 9-11, 21-24 and 28-30

The Examiner has rejected Claims 1, 4, 9-11, 21-24 and 28-30 as being unpatentable over U.S. Patent No. 4,816,449 (Hahn '449) in view of U.S. Patent No. 4,975,423 (Gaffar). It is the Examiner's position that:

> Hahn ['449] discloses (col 15, table 2) that the following peptide inhibits NK cell-induced cytotoxicity: Ala-Arg-His-Ser. Hahn ['449] does not disclose that NK cells produce ROS.
>
> Gaffar discloses (col 1, line 30+) that NK cells cause "damage" by producing reactive oxygen species. Gaffar does not disclose any peptide falling within the scope of claim 1.
>
> Thus, it would have been obvious to one of ordinary skill that by contacting the tetrapeptide A-R-H-S with NK cells, the amount of ROS produced will be reduced, and hence the "damage" caused by the ROS will be reduced also.

Applicants respectfully traverse this rejection.

Hahn '449 teaches certain peptides that modulate immune functions by binding to Fc receptors on immune cells (see, *e.g.*, column 2, line 55 through column 3, line 11, column 3, lines 35-52, column 5, lines 47-51, and column 6, line 57 through column 7, line 20). *In vitro* data are presented indicating that Ala Arg His Ser and two other peptides are able to inhibit NK

cell cytotoxicity (see Table 2). However, Hahn'449 also teaches that the peptides described in that patent may stimulate NK cell cytotoxicity (see column 3, lines 35-52). It is never explained in Hahn'449 under what conditions the peptides will inhibit and under what conditions the peptides will stimulate NK cell cytotoxicity.

Gaffar does teach that the cytolytic activity of NK cells relates to the generation of ROS (see column 1, lines 28-44). However, other references teach that the cytolytic activity of NK cells is due to degradative enzymes, cytotoxic lymphokines (perforins) and induction of apoptosis. See, *e.g.,* Herbert et al., *The Dictionary Of Immunology*, pages 50 and 119-120, Academic Press, 4th ed., 1995) (copy enclosed). See also column 3, lines 3-11 of Hahn '449. Thus, at best, the mechanism of NK cell cytotoxicity is unclear from the prior art. Further, the goal of Gaffar is to supplement the killing of undesired cells by NK cells by using non-peptide ROS-forming compounds (see, *e.g.*, column 4, lines 40-65).

Accordingly, it is unclear from the teachings of the prior art whether Ala Arg His Ser, or any of the other peptides taught by Hahn '449, would always inhibit NK cell cytotoxicity, or would only do so under certain circumstances. Also, it is unclear from the teachings of the prior art whether NK cell cytotoxicity is mediated by ROS.

Most important, however, the cited references, alone or in combination, do not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by the combined teachings of Hahn '449 and Gaffar.

For all of the foregoing reasons, the Examiner is asked to withdraw this rejection.

7. Rejection of Claims 1, 4, 9-11, 21-24 and 28-30

The Examiner has rejected Claims 1, 4, 9-11, 21-24 and 28-30 as being unpatentable over U.S. Patent No. 4,628,045 (Hahn '045) in view of U.S. Patent No. 4,975,423 (Gaffar). It is the Examiner's position that:

> Hahn discloses (col 15, table 2) that the following peptide inhibits NK cell-induced cytotoxicity: Ala-Arg-His-Ser. Hahn does not disclose that NK cells produce ROS.
>
> Gaffar discloses (col 1, line 30+) that NK cells cause "damage" by producing reactive oxygen species. . . .
>
> Thus, it would have been obvious to one of ordinary skill that by contacting the tetrapeptide A-R-H-S with NK cells, the amount of ROS produced will be reduced, and hence the "damage" caused by the ROS will be reduced also.

Applicants respectfully traverse this rejection.

Hahn '045 teaches certain peptides that modulate immune functions by binding to Fc receptors on immune cells (see, *e.g.*, column 2, line 55 through column 3, line 11, column 3, lines 27-30, column 3, line 55 through column 4, line 55, column 8, lines 43-49, column 13, line 64 through column 14, line 12). *In vitro* data are presented indicating that Ala Arg His Ser and two other peptides are able to inhibit NK cell cytotoxicity (see Table 5). However, Hahn'045 also teaches that the peptides described in that patent may stimulate NK cell cytotoxicity (see column 3, line 55 through column 4, line 55). It is never explained in Hahn'045 under what conditions the peptides will inhibit and under what conditions the peptides will stimulate NK cell cytotoxicity.

Gaffar does teach that the cytolytic activity of NK cells relates to the generation of ROS (see column 1, lines 28-44). However, other references teach that the cytolytic activity of NK cells is due to degradative enzymes, cytotoxic lymphokines (perforins) and induction of apoptosis. See, *e.g.*, Herbert et al., *The Dictionary Of Immunology*, pages 50 and 119-120, Academic Press, 4th ed., 1995) (copy enclosed). See also column 3, lines 3-11 of Hahn '045. Thus, at best, the mechanism of NK cell cytotoxicity is unclear from the prior art. Further, the

goal of Gaffar is to supplement the killing of undesired cells by NK cells by using non-peptide ROS-forming compounds (see, *e.g.*, column 4, lines 40-65).

Accordingly, it is unclear from the teachings of the prior art whether Ala Arg His Ser, or any of the other peptides taught by Hahn '045, would always inhibit NK cell cytotoxicity, or would only do so under certain circumstances. Also, it is unclear from the teachings of the prior art whether NK cell cytotoxicity is mediated by ROS.

Most important, however, the cited references, alone or in combination, do not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by the combined teachings of Hahn '045 and Gaffar.

For all of the foregoing reasons, the Examiner is asked to withdraw this rejection.

8. Rejection of Claims 1, 4, 9-10, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 4, 9-10, 21-24, 28-30 and 375-381 as being unpatentable over Heavner (PCT application WO 94/14836). It is the Examiner's position that:

> Heavner discloses (p. 26, line 21 and page 46, line 19) various peptides for treating ischemia. Among them is SEQ ID NO: 21, which is the following: SKHKLALCY (see, e.g., page 10, line 32; page 24, line 25).
>
> The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of the ischemia.
>
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Heavner teaches the use of certain peptides, including the specific SKHKLALCY peptide, to inhibit the binding of selectins, such as P-selectin, E-selectin and L-selectin (see page 1, lines 3-5 and page 7, line 28 through page 9, line 17). As a consequence of this ability, the peptides are taught by Heavner to be effective in treating ischemia and reperfusion (see page 26, line 5 through page 27, line 13).

However, Heavner does not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by Heavner.

Accordingly, the teachings of Heavner would not have made the claimed invention obvious, and the Examiner is asked to withdraw this rejection.

9. Rejection of Claims 1, 4, 9-10, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 4, 9-10, 21-24, 28-30 and 375-381 as being unpatentable over Heavner (PCT application WO 94/14836) in view of Moyle (U.S. Patent No. 5,919,900) or Nierman (U.S. Patent No. 5,529,907) or Serhan (U.S. Patent No. 6,008,205) . It is the Examiner's position that:

> Heavner discloses (p. 26, line 21 and page 46, line 19) various peptides for treating ischemia. Among them is SEQ ID NO: 21, which is the following: SKHKLALCY (see, e.g., page 10, line 32; page 24, line 25). It is also disclosed that the peptides inhibit binding of neutrophils to P-selectin. In the "backround" [sic, background] section of Heavner, it is disclosed that compounds acting by the same mechanism as the disclosed peptides inhibit the binding of neutrophils to endothelium. Heavner does not disclose that neutrophils produce ROS. Each of Moyle, Nierman and Serhan disclose the neutrophils produce ROS. (See, e.g., col 1, line 34+ [of] Serhan; col

2, line 65+ of Nierman; and several locations of Moyle such as col 1, line 45+ and col 2, line 60).

One of ordinary skill in possession of the references would determine that the peptides of Heavner will reduce the recruitment of neutrophils to the site of injury, and hence the "damage" caused by the neutrophils at that site will be reduced.

Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Heavner teaches the use of certain peptides, including the specific SKHKLALCY peptide, to inhibit the binding of selectins, such as P-selectin, E-selectin and L-selectin (see page 1, lines 3-5 and page 7, line 28 through page 9, line 17). In particular, as contended by the Examiner, Heavner teaches that the peptides can inhibit the binding of neutrophils to P-selectin (see, *e.g.*, page 9, lines 12-17). However, Applicants can find no teaching in the Background section of Heavner that compounds that inhibit the binding of neutrophils to P-selectin would also inhibit the binding of neutrophils to endothelium, as contended by the Examiner (see page 4, line 28 through page 4, line 9).

Moyle, Nierman and Serhan do teach that neutrophils produce ROS under certain conditions at sites of injury or infection (see column 1, line 41 through column 3, line 20 of Moyle, column 1, line 34 through column 2, line 17 of Serhan and column 2, line 17 through column 3, line 13 of Nierman).

However, the combined teachings of Heavner with those of Moyle, Nierman and/or Serhan do not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using

peptide P_1 - P_2 is not taught or suggested by the combined teachings of Heavner and Moyle, Nierman and/or Serhan.

Accordingly, the combined teachings of Heavner and Moyle, Nierman and/or Serhan would not have made the claimed invention obvious, and the Examiner is asked to withdraw this rejection.

10. Rejection of Claims 1, 9, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 9, 21-24, 28-30 and 375-381 as being unpatentable over Saitoh (PCT application WO 94/09808). It is the Examiner's position that:

> Saitoh discloses various peptides for treating neurological disease, or ischemia (e.g., col 6, line 21). Among the peptides asserted to be effective in this regard is the peptide designated SEQ ID NO:8 (see page 18 and page 40). The sequence of this peptide is the following: AK**H**RERMSQVM
>
> The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of the ischemia.
>
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Saitoh teaches certain peptides, including AKHRERMSQVM, for use in promoting the growth and regeneration of neurons (see, *e.g.*, page 4, line 34 through page 7, line 12, and page 11, lines17- 31). As a consequence, they can be used in the treatment of brain disorders, including ischemia and hypoxia.

The Examiner contends that, since the AKHRERMSQVM peptide can be used to treat ischemia, a person of ordinary skill in the art "would reason that . . . the compound is also effective to reduce the 'damage' that results in the manifestations of the symptoms of ischemia." The Examiner does not specify what is the "damage." Presumably, the Examiner is referring to the damage done by ROS. However, the Examiner does not provide any evidence, cite to prior art or even explain how the damage done by ROS "results in the manifestations of the symptoms of ischemia." Further, there is no teaching or suggestion in Saitoh that the AKHRERMSQVM

peptide, or any of the others taught by that patent, reduces ROS or the damage done by ROS. In fact, Saitoh does not teach or suggest anything about ROS.

Quite clearly, then, the Examiner has provided no evidence based on the prior art to support his contention, which he must do, and it is submitted that the Examiner has improperly reconstructed the claimed invention through hindsight using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner has not met in this case.

Most important, Saitoh does not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by Saitoh.

For all of the foregoing reasons, the teachings of Saitoh would not have made the claimed invention obvious, and the Examiner is asked to withdraw this rejection.

11. Rejection of Claims 1, 9, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 9, 21-24, 28-30 and 375-381 as being unpatentable over Saitoh (PCT application WO 94/09808) in view of Hensley (*Ann N.Y.Acad. Sci.*, **786**:120-134 (1996)). It is the Examiner's position that:

> Saitoh discloses various peptides for treating neurological disease such as Alzheimer's. Among the peptides asserted to be effective in this regard is the peptide designated SEQ ID NO:8 (see page 18 and page 40). The sequence of this peptide is the following:

AKHRERMSQVM

Saitoh does not disclose that Alzheimer's Disease is mediated by ROS. However, Hensley discloses that Alzheimer's Disease is mediated by ROS.

Thus, the artisan of ordinary skill would reason that if a compound is effective to treat Alzheimer's Disease, then the compound is also effective to reduce the "damage" that is caused in patients afflicted with the disorder.

Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Saitoh teaches certain peptides, including AKHRERMSQVM, for use in promoting the growth and regeneration of neurons (see, *e.g.*, page 4, line 34 through page 7, line 12). As a consequence, they can be used in the treatment of brain disorders, including Alzheimer's disease. As noted above, Saitoh does not teach or suggest that the peptides reduce ROS or the damage done by ROS. Indeed, Saitoh does not teach or suggest anything about ROS.

Hensley does suggest that ROS are involved in Alzheimer's disease. Hensley does not teach or suggest anything about neuronal growth factors.

As can be readily seen from the foregoing, the Examiner has provided no teaching, suggestion or motivation for combining the teachings of Saitoh with those of Hensley. In particular, as noted above, Saitoh does not teach or suggest anything about ROS, and Hensley does not teach or suggest anything about neuronal growth factors. Presumably, the Examiner's rationale for choosing the cited references was that they all deal with the subject of Alzheimer's disease. However, why didn't the Examiner choose a reference discussing the role of another factor in Alzheimer's disease, instead of Hensley which discusses the role of ROS in Alzheimer's disease?

It is submitted that the only basis for combining the teachings of Saitoh with those of Hensley is improper hindsight reconstruction of the claimed invention by the Examiner using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be

reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner could not meet in this case.

Most important, however, the cited references, alone or in combination, do not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested Saitoh in combination with Hensley.

For all of the foregoing reasons, the Examiner is asked to withdraw this rejection.

12. Rejection of Claims 1, 9-11, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 9-11, 21-24, 28-30 and 375-381 as being unpatentable over Chen *et al.*, *Food Factors for Cancer Prevention, International Conference on Food Factors: Chemisty and Cancer Prevention, Hamamatsu, Japan, Dec., 1995* (1997), Meeting Date 1995, 639-641; Editor(s): Ohigashi, Hajime; Publisher: Springer, Tokyo, Japan ("Chen 1997") or Chen *et al., J. Agric. Food Chemistry*, **46**(1):49-53 (1998) ("Chen 1998"). It is the Examiner's position that:

> Chen (1998) discloses (table 1 page 51) that various histidine-containing tripeptides and tetrapeptides inhibit the production of ROS. This is also disclosed on page 640 of Chen (1997). Accordingly, a chemist of ordinary skill would reason that if the production of ROS can be inhibited, the "damage" caused by ROS will be reduced.
>
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Chen 1997 and Chen 1998 describe the *in vitro* testing of the antioxidative activity of several peptides, some of which contain histidine as the third amino acid. In particular, Chen

1997 describes the testing of the peptides in an *in vitro* assay for oxidative activity that is performed under nonphysiological conditions (*e.g.*, high ethanol concentration and 60°C) (see last full paragraph on page 639 of Chen 1997). Chen 1998 describes the testing of the peptides in several *in vitro* assays. All of these assays that are described in Chen 1998 are performed under nonphysiological conditions (*e.g.*, high ethanol concentration, presence of surfactant and/or temperatures other than 37°C) (see Materials And Methods section, first and second columns, page 50, of Chen 1998). The conditions for one assay, the scavenging of superoxide, are not described in Chen 1998, but the peptides did not exhibit oxidative activity in this assay (see Table 1 and first full paragraph, second column, page 51, of Chen 1998).

The rejected claims are directed to the use of the P_1 - P_2 peptides *in vivo* to reduce the damage done by ROS. There is certainly nothing about the results of the Chen 1997 and/or Chen 1998 *in vitro* assays performed under nonphysiological conditions that would have suggested to those skilled in the art that the Chen peptides could be expected to have antioxidative activity *in vivo*. Thus, neither Chen 1997, nor Chen 1998, teaches or suggests that the peptides described in those references can be used *in vivo* to reduce the damage done by ROS.

In addition, Chen 1998 reports that the metal ion chelating activity of the peptides described in that reference did not correlate to their antioxidative activity (see, *e.g.*, abstract of Chen 1998, page 49). In contrast, in the method of the present invention, the damage done by ROS is reduced as a result of the binding of metal ions by the P_1 - P_2 peptides. This is the opposite of what is reported in Chen 1998, and Chen 1998, therefore, teaches away from the claimed invention.

For the foregoing reasons, Chen 1997 and/or Chen 1998 would not have made the claimed invention obvious, and this rejection should be withdrawn.

13. Rejection of Claims 1, 9-10, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 9-10, 21-24, 28-30 and 375-381 as being unpatentable over Morikawa (*Stroke*, **27**(5):951-956 (1996)) or Seko (*Journal of Pathology*, **178**(3):335-342 (1996)). It is the Examiner's position that:

> Morikawa discloses the following peptide (p. 952, col 1, line 2): YTHLVAIQ This peptide is also disclosed in Seko (page 336, col 1, line 6). Both references disclose that the peptide is effective to treat ischemia. One of ordinary skill would have reasoned that if a peptide is effective to treat ischemia, the "damaging" effects that gave rise to the symptoms of ischemia would be reduced.

Applicants respectfully traverse this rejection.

Morikawa teaches that the peptide YTHLVAIQ blocks selectin-mediated cell adhesion and is effective in treating transient, but not permanent, cerebral ischemia (see abstract, page 951). Seko teaches that the same peptide blocks selectin-mediated cell adhesion and is effective for the treatment of transient myocardial ischemia and hypoxia (see abstract, page 335).

The Examiner contends that, since the YTHLVAIQ peptide can be used to treat ischemia, a person skilled in the art "would have reasoned that if a peptide is effective to treat ischemia, the 'damaging' effects that give rise to the symptoms of ischemia would be reduced." The Examiner does not specify what are the "damaging effects." Presumably, the Examiner is referring to the damage done by ROS. However, the Examiner does not provide any evidence, cite to prior art or even explain how the damage done by ROS "gives rise to the symptoms of ischemia."

It is submitted that the Examiner has improperly reconstructed the claimed invention through hindsight using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner has not met in this case.

More important, neither Morikawa nor Seko teaches or suggests the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by Morikawa or Seko. For all of the foregoing reasons, the teachings of Morikawa or Seko would not have made the claimed invention obvious, and the Examiner is asked to withdraw this rejection.

14. Rejection of Claims 1, 9-10, 21-24, 28-30 and 375-381

The Examiner has rejected Claims 1, 9-10, 21-24, 28-30 and 375-381 as being unpatentable over Kaplan (*Neuroscience Research Communications*, **19**(2):115-123 (1996)). It is the Examiner's position that:

> Kaplan discloses that the following peptide is effective to treat one or more symptoms of ischemia: MEHFPGP
>
> The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of ischemia.
>
> Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Kaplan teaches that the peptide MEHFPGP is a modulator of memory processes and other cognitive functions (see first full paragraph of the text on page 115). It was also found to have a positive effect on EEG during an acute hyperventilation model of transient ischemia (see Table 1, page 1. This is attributed to its antihypoxic effect (see Discussion on page 122 and second full paragraph of the text on page 115).

The Examiner contends that, since the MEHFPGP peptide can be used to treat ischemia, an "artisan of ordinary skill would reason that . . . the compound is also effective to reduce the 'damage' that results in the manifestations of the symptoms of ischemia." The Examiner does not specify what is the "damage." Presumably, the Examiner is referring to the damage done by ROS. However, the Examiner does not provide any evidence, cite to prior art or even explain how the damage done by ROS "results in the manifestations of the symptoms of ischemia."

In any event, there is no teaching or suggestion in Kaplan that the MEHFPGP peptide reduces ROS or the damage done by ROS. In fact, Kaplan does not teach or suggest anything about ROS. However, since the MEHFPGP peptide appears to increase, or at least maintain, oxygen levels in the brain (antihypoxic effect), it is possible that its use would actually increase ROS, instead of reducing them.

It is submitted that the Examiner has improperly reconstructed the claimed invention through hindsight using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner has not met in this case.

More important, Kaplan does not teach or suggest the claimed method. Amended Claim 1 is directed to a method of reducing the damage done by ROS in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal that cause the production and/or accumulation of ROS, with the result that the damage done by the ROS is reduced. See, *e.g.*, page 1, lines 7-13, page 13, line 19 through page 14, line 2, and Examples 7-11 and 13 of the present application. This method of reducing the damage done by ROS by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by Kaplan.

For all of the foregoing reasons, the teachings of Kaplan would not have made the claimed invention obvious, and the Examiner is asked to withdraw this rejection.

E. Information Disclosure Statements

Applicants note that the Examiner has deleted two entries from the PTO 1449 forms submitted with Applicants' previous response. These two entries referred to JP 62116565 A2. As suggested by the Examiner in the preceding Office Action, the 1449 listed the reference in the "Other Art" section since only an English abstract was available. In addition, Applicant mistakenly included the reference in the "Foreign Patent" section. No reason is given by the Examiner for deleting the reference entry in the "Other Art" section. Applicants ask that the Examiner review the reference, a copy of which was submitted, and indicate that this review has taken place by initialing the attached PTO 1449 form.

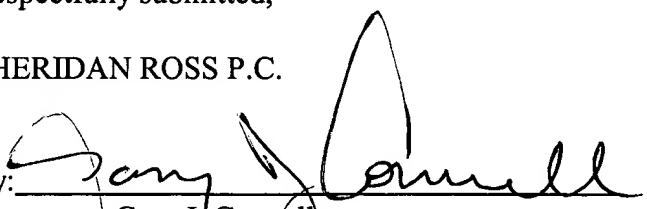
In addition, Applicants are submitting herewith another supplemental information disclosure statement disclosing two references recently cited in U.S. application number 10/076,071 which are not of record in the present case. These references are also listed on the attached PTO 1449 form.

CONCLUSION

It is respectfully submitted that the pending claims are in condition for allowance, and a speedy allowance of them is requested.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: 

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Date: Nov. 24, 2004

Amendments to the Drawings:

The attached drawing sheet includes changes to Figs. 1A - 1D. This sheet, which includes Figs. 1A - 1D, replaces the original sheet, in which the double bonds were missing from the imidazole group.

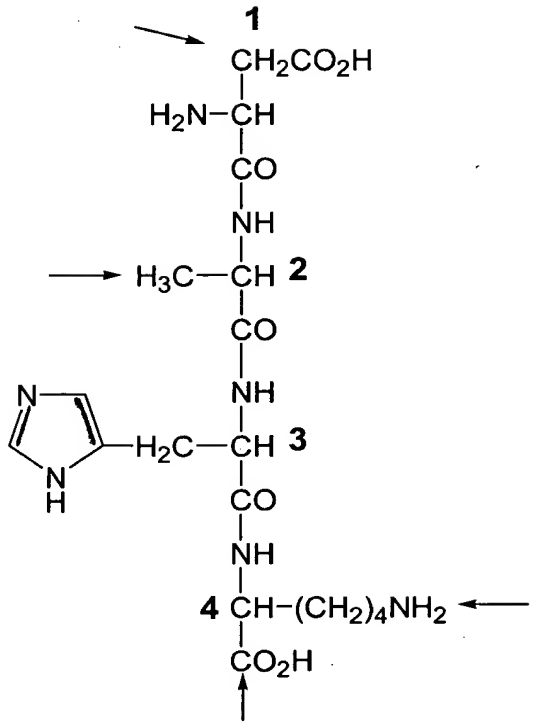

FIG. 1A

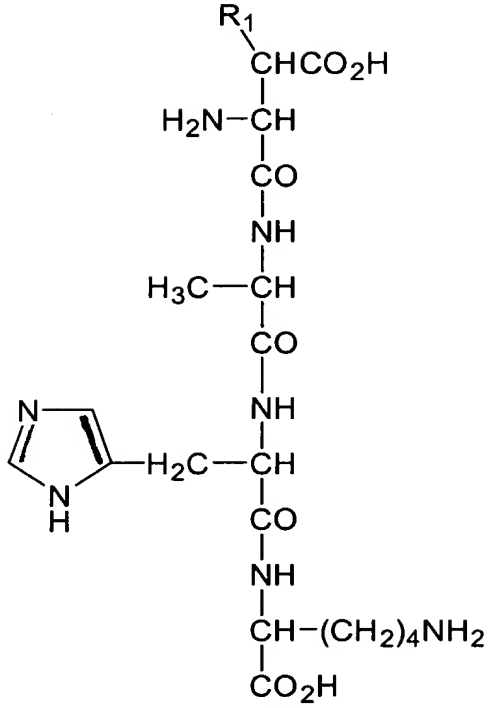

FIG. 1B

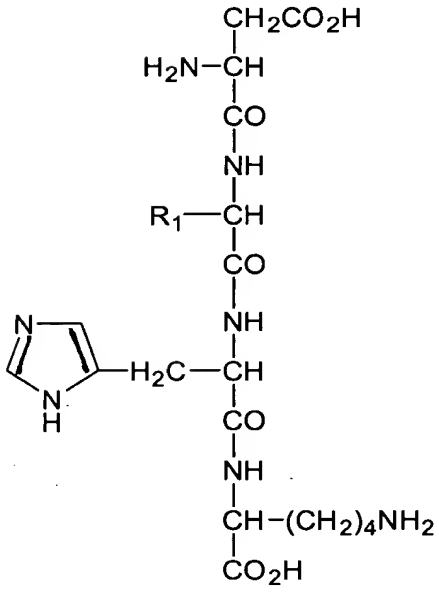

FIG. 1C

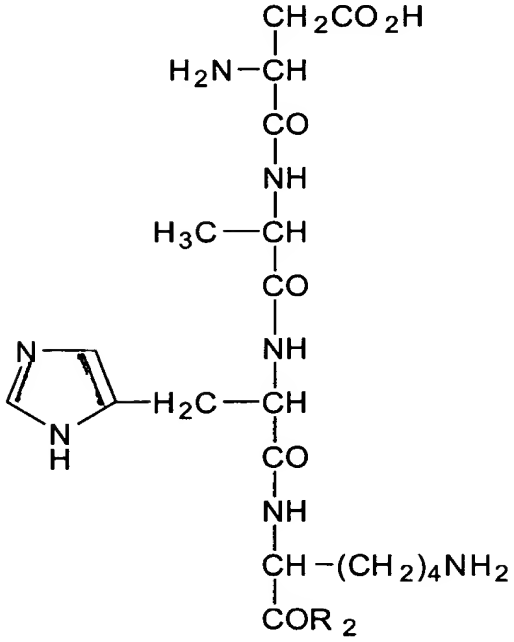

FIG. 1D